EXHIBIT 6g

This study confirmed the developmental toxicity of APAP (300μM) on rat embryos.[367] The study examined APAP and APAP metabolites by orally treating rats (1g/Kg) and monkeys (400mg/Kg) with APAP and collecting serum from animals for subsequent testing and rat embryo culture. The authors reported that APAP reduced the levels of glutathione (GSH) in the yolk sac (the tissue surrounding the embryo), and that APAP toxicity was potentiated by depletion of GSH. They also demonstrated that the addition of the glutathione precursor N-acetylcysteine (NAC) would rescue the embryos from the harmful effects of APAP. The resulting developmental toxicities from treated rats and monkeys demonstrated time dependent and concentration dependent interactions, with 70 minutes in the monkey serum, and 15 and 30 minutes in the rat serum showing the most toxicity to exposed rat embryos in culture. This study demonstrated dose-responsive developmental toxicity of APAP and metabolites thereof on cultured rat embryos (Table 10).

Treatment	Acetaminophen concentrations in culture (μM)	No. of embryos (abnormal/total)	Number of embryos: Open neutral tubes	Compressed optic vesicles	Incomplete body curvature	Embryo protein (μg/embryo ± SEM)
Acetaminophen						
	0	0/6	0	0	0	218 ± 11
	300	5/10	4	4	5	195 ± 8
	450	12/12	8	10	8	109 ± 7
	600	10/10	6	9	8	65 ± 5
	750	7/7	6	7	6	42 ± 4

Table 10. Teratogenic Effects of Acetaminophen on Cultured Rat Embryos.[367]

Gandy (1990)

This study examined several compounds for the ability to perturb glutathione (GSH) levels in the testes and epididymides as well as liver following single acute dosages to rats.[368] The authors propose a protective role for GSH in reproductive tissues, and that GSH detoxification may be critical in preventing chemical-induced germ-cell mutations. Moreover, the study indicates that the GSH detoxication system is present in male reproductive tissue, including GSH, GSH S-transferases, GSH peroxidase, GSH reductase, and gamma-glutamyl transpeptidase. The authors report that APAP (1500 mg/kg, IP) caused a decrease in hepatic GSH to 31% of control levels at 1hr post treatment, and testicular GSH was significantly depleted to 68% of controls values at 1hr. Also, while liver GSH declined from 4-18hrs, there was a recovery of testicular GSH by 2hrs posttreatment. They authors propose that lowering GSH in the male reproductive tract may be a way that chemicals can cause mutations in sperm cells.

Micheli (1994)

[367] Weeks et al. Acetaminophen toxicity to cultured rat embryos. Teratog Carcinog Mutagen. 1990;10(5):361-71. doi: 10.1002/tcm.1770100502. PMID: 1981948.

[368] Gandy et al. Effects of selected chemicals on the glutathione status in the male reproductive system of rats. J Toxicol Environ Health. 1990;29(1):45-57. doi: 10.1080/15287399009531370. PMID: 2299686.

This study examined the impact of APAP on testicular glutathione (GSH) levels.[369] This study was performed in Wistar rats and the authors report that APAP reached a peak concentration (Cmax) of 114ug/g at 6 hours post oral administration of 3g/Kg. Testicular GSH was also shown to significantly decrease to approximately 75% of controls at 4 hours post treatment. The authors propose that APAP and NAPQI exposure can produce specific toxicities in the organs and tissues exposed to these chemicals and can potentiate the toxicity of other toxic agents by reducing GSH in those tissues.

Acharya 2010

This study demonstrated that while APAP depletes glutathione, treatment with NAC, hypotaurine (HYTAU), or taurine (TAU) mitigate glutathione loss in both plasma and liver.[370]

Toyoda 2018.

This study examined genetic differences and obesity as a potential modifier of APAP-toxicity.[371] Male F344 and Zucker (lean and obese) rats were administered 0, 80, 253, 800, 2,530, or 8,000 ppm APAP in the diet for 13 weeks. There was no significant toxicity related to APAP treatment in all three strains. The body weight gain in F344 and lean Zucker rats was reduced. Other notable changes at the high dose include increased brain and liver weight in the F344 rats, and increased liver weight with decreased testicular weight in the lean Zucker rats. The results suggested that Zucker rats may be less susceptible to APAP toxicity than lean rats. As indicated below, see NTP, a 6,000ppm APAP diet results in an exposure of approximately 300mg/Kg/day, so the high dosage (8,000ppm) is expected to result in an exposure of ~400mg/Kg/day. This dosage produced no overt liver toxicity in any of the rat strains examined. The high dosage (8,000 ppm or 400mg/Kg/day), results in a HED of ~65mg/Kg or ~3.9g/day in a 60Kg human.

Koyuncuoğlu 2020

This study examined whether males have greater propensity for toxicity from APAP than females.[372] The investigators used APAP overdosing (3g/Kg, IP) in male rats and female rats that underwent ovariectomy (OVX) or sham-OVX. Results indicated the hepatotoxicity of APAP was less severe in female rats, but renal toxicity was not influenced by sex or by the lack of ovarian hormones. The authors also reported that pretreatment with estrogen or ER agonists provided protective effects against APAP-induced hepato- and renal toxicity. The antioxidant activity of estrogens was thereby supported to mitigate these and potentially other toxicities produced by APAP.

Herrington (2022)

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[369] Micheli et al. Effect of acetaminophen on glutathione levels in rat testis and lung. Environ Health Perspect. 1994 Nov;102 Suppl 9(Suppl 9):63-4. doi: 10.1289/ehp.94102s963. PMID: 7698087; PMCID: PMC1566779.

[370] Acharya and Lau-Cam. Comparison of the protective actions of N-acetylcysteine, hypotaurine and taurine against acetaminophen-induced hepatotoxicity in the rat. J Biomed Sci. 2010 Aug 24;17 Suppl 1(Suppl 1):S35. doi: 10.1186/1423-0127-17-S1-S35. PMID: 20804611; PMCID: PMC2994383.

[371] Toyoda et al. A 13-week subchronic toxicity study of acetaminophen using an obese rat model. J Toxicol Sci. 2018;43(7):423-433. doi: 10.2131/jts.43.423. PMID: 29973474.

[372] Koyuncuoğlu et al. Estrogen receptor agonists protect against acetaminophen-induced hepatorenal toxicity in rats. Life Sci. 2020 Dec 15;263:118561. doi: 10.1016/j.lfs.2020.118561. Epub 2020 Oct 10. PMID: 33045213.

A study by Herrington et al., hypothesized that exposure to ghrelin prior to exposure to APAP would mitigate the behavioral effects of APAP exposure.[373] Ghrelin is a neuroactive peptide commonly described as a signaling molecule for hunger, but it is also reported to processes antioxidant properties. The authors report that ghrelin can restore altered anxiety-associated behaviors in rats. They conclude that the results are the first to demonstrate that ghrelin can mitigate the effects of perinatal APAP exposure in rats. This study is compelling because ghrelin was given after APAP exposure, so ghrelin may have potential therapeutic benefits similar to providing NAC to patients or animals overdosed with APAP. Ghrelin is also reported to modify serotonin,[374] and influence appetite by modifying cannabin[375]signaling.[376] These various interactions indicate that the ability of ghrelin to rescue disrupted neurodevelopment caused by APAP may be due to modified oxidative stress and convergent signaling interactions between APAP and ghrelin.

4. Studies Examining Acetaminophen and Biological Changes in Reproductive or Other Tissues.

In addition to the rat studies described above that examined biological changes to the brain, rat studies were used to examine whether APAP caused biological changes in reproductive or other tissues.

Momma 1983

This study examined numerous chemicals and medications, including APAP, for impacts on fetal ductal constriction.[377] Wistar rat dams were exposed to APAP at doses of 10, 100, or 1000 mg/Kg. Transverse sections of the main pulmonary artery (PA) and the ductus arteriosus (DA) were examined, and measured diameters were used calculate a DA/PA ratio for each chemical (Figure 30). APAP at higher doses induced ductal constriction. This impact of APAP on the ductus arteriosus is consistent with clinical studies and was summarized in recent reviews on the treatment or closure of patent ductus arteriosus (PDA) in infants.[378] This activity is proposed to be due to inhibition of cyclooxygenases.

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[373] Herrington et al. Elevated ghrelin alters the behavioral effects of perinatal acetaminophen exposure in rats. Dev Psychobiol. 2022 Mar;64(3):e22252. doi: 10.1002/dev.22252. PMID: 35312061.

[374] Brunetti et al. Effects of ghrelin and amylin on dopamine, norepinephrine and serotonin release in the hypothalamus. Eur J Pharmacol. 2002 Nov 15;454(2-3):189-92. doi: 10.1016/s0014-2999(02)02552-9. PMID: 12421646.

[375] Burdyga et al. Ghrelin receptors in rat and human nodose ganglia: putative role in regulating CB-1 and MCH receptor abundance. Am J Physiol Gastrointest Liver Physiol. 2006 Jun;290(6):G1289-97. doi: 10.1152/ajpgi.00543.2005. Epub 2006 Jan 19. PMID: 16423919.

[376] Fride et al. Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood. Exp Biol Med (Maywood). 2005 Apr;230(4):225-34. doi: 10.1177/153537020523000401. PMID: 15792943.

[377] Momma and Takeuchi. Constriction of fetal ductus arteriosus by non-steroidal anti-inflammatory drugs. Prostaglandins. 1983 Oct;26(4):631-43. doi: 10.1016/0090-6980(83)90200-9. PMID: 6658007.

[378] Jasani et al. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2022 Dec 15;12:CD010061. doi: 10.1002/14651858.CD010061.pub5. PMID: 36519620.

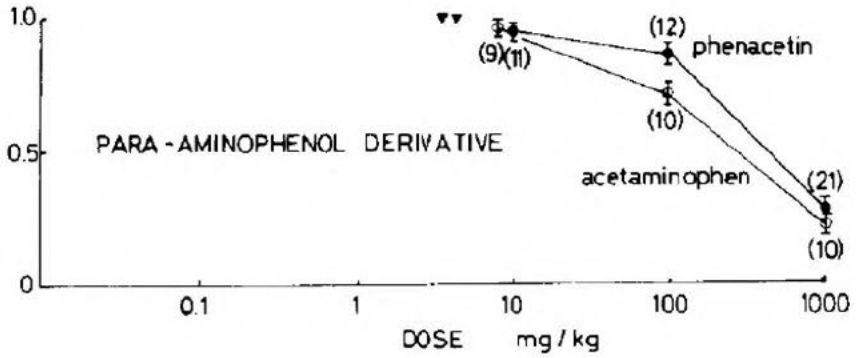

Figure 30. Fetal Ductal Constriction Caused by Acetaminophen. The main pulmonary artery (PA) and the ductus arteriosus (DA) inner diameters were measured (DA/PA ratio) for APAP and phenacetin. APAP induces ductal constriction, as indicated by a decreasing DA/PA ratio at increasing dosages of APAP.

NTP 1993

The NTP performed studies on mice and rats.[379] These studies were conducted by administering APAP in feed to F344/N rats of each sex for 14 days, 13 weeks, and 2 years. The 13-week exposure study reports,

> Acetaminophen-related lesions were observed in the liver (necrosis, chronic active inflammation, hepato- cytomegaly), kidney (tubule cast, tubule necrosis, tubule regeneration), reproductive organs (atrophy of testis, ovary, and uterus), thymus and lymph nodes (lymphoid depletion) of rats that received 25,000 ppm, and of the liver (chronic active inflammation, hepatocytomegaly) and testis (atrophy) of male rats receiving 12,500 ppm.

The NTP reports testicular atrophy at 6200, 12500, and 25000, and these results are summarized as follows,

> Testicular atrophy was observed in all male rats that received 25,000 ppm and in one male from each of the 6,200 and 12,500ppm groups. In the most severe cases, the lesion consisted of nearly complete loss of the germinal epithelium and was usually associated with complete absence of sperm in the epididymis. Atrophy of the uterus and ovary was observed in female rats that received 25,000ppm. The atrophic ovaries were small and had fewer follicles and corpora lutea, while atrophic uteri appeared small on gross observation.

Based on food consumption, the NTP reports that 6000ppm results in an exposure of approximately 300mg/Kg/day, so the foods formulated with 12,500ppm and 25,000ppm result in exposures of ~625mg/Kg/day and ~1250mg/Kg/day, respectively. The HEDs (Table 1) for these dosages (300, 625, 1250mg/Kg) are ~50mg/Kg/day, ~100mg/Kg/day, and ~200mg/Kg/day, making reference human (60Kg) exposures of 3g/day, 6g/day, and 12g/day, respectively.

Lister 1995, Lister 1997

[379] National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Acetaminophen (CAS No. 103-90-2) in F344 Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 1993 Jan;394:1-274. PMID: 12637965.

This pair of studies investigated the effects of acetaminophen on DNA synthesis.[380,381] The first of these studies used dosages of 0, 125, 500mg/Kg exposed orally to male rats. DNA synthesis was measured in various organs and tissues by incorporation of labeled thymidine. At 125mg/Kg APAP, DNA synthesis in the rat testis was almost halved (8.5 versus 16.1 DPM/mg, 53%) one hour post treatment, and at 500mg/Kg the incorporation was almost 1/10 of control (1.7 versus 16.1 DPM/mg, 11%). The second study analyzed additional dosages and tissues, and all tested tissues showed reduced DNA synthesis following APAP exposure of ≥125mg/Kg (Table 11). This study indicates that DNA synthesis in the testis was less than half of controls at 125mg/Kg. (24.3 versus 10.9 DPM/mg). The 500mg/Kg dosage (HED 80mg/Kg, 4.8g) was reported to result in a plasma concentration of ~600μM, and a urine concentration of >9mM, 1 hour post treatment.

		Thymidine incorporation		DPM/ mg tissue	
Tissue	Control ($n = 9$)	60 mg/kg Para ($n = 3$)	125 mg/kg Para ($n = 4$)	500 mg/kg Para ($n = 4$)	1 g/kg Para ($n = 3$)
Stomach squamous	32.5 ± 16.0	19.4 ± 9.4	–	8.7 ± 1.6*	8.0 ± 0.8*
Stomach glandular	48.2 ± 12.3	47.6 ± 9.0	17.9 ± 4.1*	28.7 ± 14.8	26.2 ± 4.5*
Duodenum	129.0 ± 42.4	138.2 ± 29.3	62.9 ± 59.3*	58.1 ± 8.7*	35.2 ± 8.7*
Jejunum	223.7 ± 41.9	190.5 ± 43.7	116.1 ± 66.7*	62.0 ± 23.5*	45.2 ± 16.3*
Liver	40.4 ± 10.2	35.3 ± 13.2	27.3 ± 5.2*	44.5 ± 7.8	39.5 ± 2.2
Kidney	36.0 ± 8.3	33.3 ± 5.1	14.5 ± 3.2*	23.7 ± 4.9*	20.9 ± 1.4*
Testis	23.6 ± 7.6	24.3 ± 9.2	10.9 ± 4.9*	8.1 ± 1.8*	

Table 11. Inhibition of DNA Synthesis by Acetaminophen (Para) in Male Rats. Mean +/- SD for n separate animals. *Denotes P<O.05 as compared to the control values.[381]

Ratnasooriya (2000)

This study examined the effect of acetaminophen on the ability of male rats to reproduce.[382] The rats were given APAP (0, 500, 1000mg/Kg) orally for 30 days, and sexual behavior and fertility were tested at 2 hours after first treatment, at 30 days of treatment, and 30 days post treatment. The results showed that the rats given APAP had decreased mating and reproductive fitness (fertility index and implantation index), and this was associated with decreased sperm counts. The effect was reversible and not due to overt morbidity. The authors propose that this study supports that taking high doses of APAP for extended periods of time may reduce the ability of men to father children.

Neto (2004)

Neto et al. (2004) gave APAP (150, 500 or 1,500 mg/kg, once a day by gavage) throughout gestation (GD1-20) to pregnant Wistar rats.[383] The rats at 150mg/Kg had no reported hepatic or renal pathology,

[380] Lister and McLean. Differential inhibition of DNA synthesis by paracetamol in the rat testis and GI tract. Biochem Soc Trans. 1995 May;23(2):265S. doi: 10.1042/bst023265s. PMID: 7672290.
[381] Lister and McLean. Inhibition of DNA synthesis by paracetamol in different tissues of the rat in vivo. Toxicology. 1997 Jan 15;116(1-3):49-57. doi: 10.1016/s0300-483x(96)03521-4. PMID: 9020506.
[382] Ratnasooriya and Jayakody. Long-term administration of large doses of paracetamol impairs the reproductive competence of male rats. Asian J Androl. 2000 Dec;2(4):247-55. PMID: 11202412.
[383] Neto et al. Long-term acetaminophen (paracetamol) treatment causes liver and kidney ultra-structural changes during rat pregnancy. Clin Exp Obstet Gynecol. 2004;31(3):221-4. PMID: 15491069.

but the rats given 500 or 1500mg/Kg had liver and kidney pathologies. The authors conclude that both maternal and fetal tissues can be adversely affected by APAP.

Oyedeji (2013)

This study examined the effects of oral administration of paracetamol on hematological parameters (30 days) and reproductive parameters (21 days) in female albino rats.[384] APAP was administered by gavage at 7.5mg/Kg for 30 or 21 days based on the study endpoints. There were no significant hematological changes in the RBC, PCV, Hb, TWBC, platelet, neutrophil, lymphocyte, eosinophil, monocyte and MCH values. The duration of all phases of estrous cycle was also unaffected by the treatment of rats with APAP. The findings show that there is no effect on the blood chemistry or fertility of female albino rats at the 7.5mg/Kg/day dosage. This dosage produces a HED of 1.2mg/KG, which would be about 75mg in a 60Kg adult—only a fraction of a single recommended dose of 1000mg.

Axelstad (2014) and Kristensen (2011)

Axelstad et al (2014) reported the impact of 13 endocrine-disrupting contaminants, including pesticides, plastic and cosmetic ingredients, and APAP on Wistar rats.[385] The study examined endpoints or adverse reproductive effects, and these included decreased anogenital distance (AGD), increased nipple retention (NR), and weights of the levator ani/bulbocavernosus muscle (LABC). To avoid problems with parturition, APAP treatment (350mg/kg per day) was from GD13-19 and then reinitiated on PD14-22. The authors report that APAP exposure resulted in a significant increase in NR and reduced the weight of LABC. They also reported a non-significant reduction in AGD by 1.6%. Regarding this latter impact, the authors referenced their earlier study that indicated APAP resulted in an average reduction of 4–7% reduced AGDI in fetal rat offspring on GD 21,[386] and proposed,

> This disagreement could, however, be explained in terms of a shortened exposure duration of 7 days in this study (GD 13–19), compared with 15 days in the previous one (GD 7–21) and a different age of examination.

The dosage used in these studies (350mg/Kg) produces a HED of 56.5mg/Kg, or 3.4g in a 60Kg adult, which is 3.4 times a single 1000mg human therapeutic dose.

Johansson (2016)

This study examined the impact on female reproductive organs of rats exposed *in utero* and postnatally to APAP (at 360 mg/Kg).[387] In pre-pubertal rats, the authors report that there was a reduction in primordial follicle numbers due to APAP exposures. In mature dams (1yr), they also reported decreased ovary

[384] K.O, Oyedeji. "Evaluation of Haematological and Reproductive Effect of Paracetamol (Acetaminophen) In Female Abino Rats." IOSR Journal of Dental and Medical Sciences 3.5 (2013): 72–75. Web.
[385] Axelstad M, et al. Mixtures of endocrine-disrupting contaminants induce adverse developmental effects in preweaning rats. Reproduction. 2014 Mar 2;147(4):489-501. doi: 10.1530/REP-13-0447. PMID: 24298046.
[386] Kristensen et al. Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. Hum Reprod. 2011 Jan;26(1):235-44. doi: 10.1093/humrep/deq323. Epub 2010 Nov 8. PMID: 21059752.
[387] Johansson et al. Perinatal exposure to mixtures of endocrine disrupting chemicals reduces female rat follicle reserves and accelerates reproductive aging. Reprod Toxicol. 2016 Jun;61:186-94. doi: 10.1016/j.reprotox.2016.03.045. Epub 2016 Apr 2. PMID: 27049580.

weights and suggest that their findings resemble premature ovarian insufficiency in humans and raise concerns regarding female reproductive function due to perinatal APAP exposures.

Hurtado-Gonzalez et al. (2018)

This study used multiple *in vitro* and *in vivo* models to examine the impact of APAP of gonadal cells and tissues.[388] They used first-trimester human fetal testes and ovaries for *in vitro* testing. They also incorporated second-trimester fetal germ cells in rats to produce a xenograft model. The number of gonocytes was reduced relative to controls in first-trimester human fetal testes and ovaries exposed to APAP. After treatment of xenograft host mice for one day or seven days, APAP reduced gonocyte number by up to 30%. The expression of GC pluripotency genes and genes that regulate DNA/histone methylation were altered by APAP. The authors report consistently increased expression of the epigenetic regulator TET1 in APAP exposed human NTera2 cells, rat fetal testis/ovary cultures, and in fetal testes and ovaries. They conclude that these results raise concerns about the use of APAP during human pregnancies.

Yilmaz (2020)

This study showed that *in utero* exposure of rats to APAP (50, 125, 250, 500mg/Kg) throughout gestation (GD1-20) produced various changes in the fetal liver.[389] Specifically, vascular endothelial growth factor A (VEGF-A) and FETU-A (FETUIN-A) had increasing responses from 0-500mg/Kg and Sclerostin (SOST) significantly increased at 125 and 250, but fell at 500mg/Kg.

Pereira (2020)

A study design similar to Klein 2020 was used by Pereira et al. to examine the impact of *in utero* exposure (GD6-21) versus perinatal exposure (GD6-PND21) to APAP (350 mg/kg/day) on the sexual behavior of adult male rats.[390] There was no overt toxicity with this treatment and no statistical difference between the reproductive organs, kidneys, adrenals, liver, or pituitary weight in all ages. There were also no statistical differences observed in the sperm count, morphology, or spermatic motility. The authors did report significantly increased testosterone levels, volumes and total lengths of the seminiferous tubules in both gestational and perinatal APAP exposed groups at PND 120. The authors conclude that maternal exposure to APAP has an impact on the reproductive system and sexual behavior of male adult offspring and may impair sexual hypothalamic differentiation during brain development.

Aleixo (2020)

[388] Hurtado-Gonzalez et al. Effects of Exposure to Acetaminophen and Ibuprofen on Fetal Germ Cell Development in Both Sexes in Rodent and Human Using Multiple Experimental Systems. Environ Health Perspect. 2018 Apr 16;126(4):047006. doi: 10.1289/EHP2307. PMID: 29665328; PMCID: PMC6071829.

[389] Yilmaz S, Göçmen YA, Tokpınar A. et al. Effects of Paracetamol on Vascular Endothelial Growth Factor, Sclerostin and FETUIN-A in the Liver of Rat Fetuses. Acta Med. Alanya 2020;4(2):150-155. doi:10.30565/medalanya.688286

[390] Pereira et al. Can maternal exposure to paracetamol impair reproductive parameters of male rat offspring? Reprod Toxicol. 2020 Apr;93:68-74. doi: 10.1016/j.reprotox.2019.12.007. Epub 2020 Jan 9. PMID: 31926975.

Aleixo et al. performed a study on pregnant Wistar rats gavaged daily with APAP (350mg/Kg) or water from GD6 until delivery. Maternal APAP treatment resulted in increased grooming behavior. Impacts on offspring included impaired sexual behavior and decreased egg follicle reserve in female offspring.[391]

5. Other Acetaminophen Rat Studies

In this section, I briefly describe several rat studies involving acetaminophen that do not fall into the other categories above.

Lubawy 1977

This study tested the effects of aspirin and APAP (0, 125, 250mg/Kg) on pregnant rats.[392] The medications were given to the rats by gavage for 12 days during pregnancy (GD8-19). The animals were terminated on GD20, and the researchers determined fetal and placenta weights. The was no reported gross pathology. Litters from the rats given acetaminophen at 125mg/Kg had an increased incidence of resorptions (16% vs 0% in controls) and the pups were also smaller in length at this dosage. The higher dosage of APAP showed non-significant increases in pregnancy weights for dams and fetuses, and resorptions were not increased. The authors suggest caution for interpretation of the results in humans, and report that APAP produced adverse effects relative to controls, but these were less severe than those observed with aspirin.

Lin 1983

This study examined the pharmacokinetics of APAP in pregnant versus non-pregnant rats at two dosages, 15 and 300mg/Kg given IV.[393] The researchers treated the pregnant rats on GD20 and collected blood and urine samples to examine APAP metabolites. The authors found that pregnant rats processed the 300mg/Kg dose of APAP differently than non-pregnant rats, with a longer half-life and slower clearance (Figure 31). Pregnant rats also excreted more unmetabolized APAP, produced less APAP-sulfate and the same fraction of APAP-glucuronide as did nonpregnant animals. However, pregnancy was not reported to affect the base-line serum inorganic sulfate concentration. The investigators also reported that both non-pregnant and pregnant rats became inorganic sulfate-depleted at the 300 mg/kg dosage. This dosage in rats produces a HED of ~48mg/Kg, or ~3g for a 60Kg reference adult human. Overall, this study indicates that pregnancy can affect how the body metabolizes APAP.

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[391] Aleixo et al. Effect of paracetamol treatment on maternal care and reproductive outcomes in female rat offspring. Reprod Fertil Dev. 2020 Dec;32(18):1311-1325. doi: 10.1071/RD20007. PMID: 33308393.

[392] Lubawy and Garrett. Effects of aspirin and acetaminophen on fetal and placental growth in rats. J Pharm Sci. 1977 Jan;66(1):111-3. doi: 10.1002/jps.2600660129. PMID: 833724.

[393] Lin and Levy. Effect of pregnancy on the pharmacokinetics of acetaminophen in rats. J Pharmacol Exp Ther. 1983 Jun;225(3):653-9. PMID: 6602874.

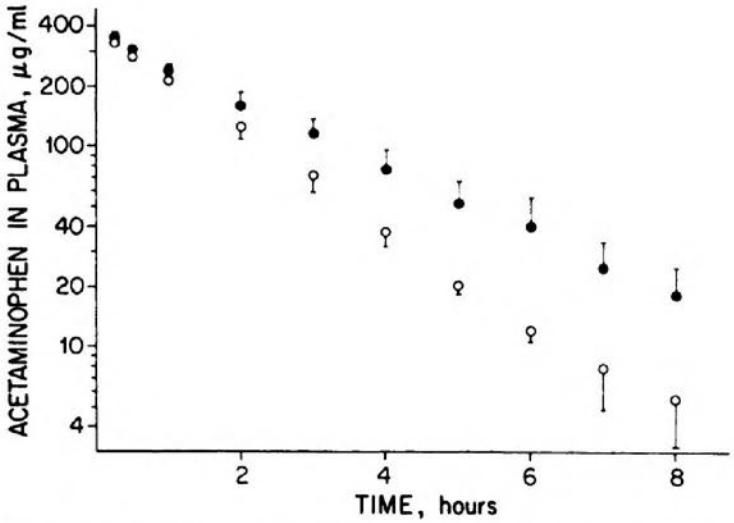

Figure 31. Acetaminophen Metabolism in Pregnant Rats. Acetaminophen concentrations in plasma of 20 days pregnant rats (●) and nonpregnant female rats (○) after i.v. injection of 300 mg/kg. Vertical bars represent 1 S.D. n=7/group.[393]

Koehn (2021)

Adenosine triphosphate binding cassette (ABC) transporters are involved in drug pharmacokinetics and can support homeostatic cellular functioning by removing certain molecules and metabolites from a cell. They can also limit the access of drugs to active sites located within a cell or restrict the transport of drugs across cellular interfaces. By maintaining desirable concentrations of substrate molecules in different areas of the body, these transporters perform endogenous functions and provide protection from a range of xenobiotics.[394] The Koehn et al. study examined whether *in utero* APAP exposure had effects on ABC transporters.[395] The investigators administered APAP (IP) twice daily to Sprague-Dawley rats from embryonic day E15 to E19 (chronic) or as a single dose at E19 (acute) at 3.75mg/Kg or 15mg/Kg. RNAseq analysis identified transcripts for ABC transporters and enzymes in rat E19, P5, and adult brain and choroid plexus and E19 placenta. The results showed that the transcription of many ABC transporters was higher in the adult brain of rats exposed to APAP *in utero*. Chronic exposure also resulted in increased APAP in the brain (E19, high dose) and plasma of dams and fetuses (E19, high dose). The authors conclude that the transfer of APAP from blood to brain differs by developmental timing, dose, and duration.

E. Hamster and Non-Rodent Animal Studies

The study by Rutkowski and Ferm (1982) evaluated the teratogenic effects of the isomeric forms of aminophenol (para-AP/p-AP, meta-AP/m-AP, and ortho-AP/o-AP) in Syrian golden hamsters.[396] As indicated previously, p-AP is a metabolite of APAP, that can be metabolized into AM404, a modifier of cannabinoid signaling (see **Cannabinoid Interactions**, above). The hamsters were given a dose of 100 to

[394] Higgins. ABC Transporters: Physiology, Structure and Mechanism – an Overview. Research in microbiology 152.3 (2001): 205–210. Web.

[395] Koehn et al. Efflux transporters in rat placenta and developing brain: transcriptomic and functional response to paracetamol. Sci Rep. 2021 Oct 6;11(1):19878. doi: 10.1038/s41598-021-99139-6. PMID: 34615937; PMCID: PMC8494792.

[396] Rutkowski and Ferm. Comparison of the teratogenic effects of the isomeric forms of aminophenol in the Syrian golden hamster. Toxicol Appl Pharmacol. 1982 Apr;63(2):264-9. doi: 10.1016/0041-008x(82)90048-5. PMID: 7089975.

200 mg/kg of p-AP, m-AP, or o-AP on Day 8 of gestation and were terminated on Day 13. The study reported that p-AP and o-AP produced a significant dose-responsive teratogenic response, with an increase in the frequency of litters with one or more malformed fetuses and an increase in the number of fetuses with one or more malformations as the dose increased. Common malformations observed included exencephaly, encephalocele, eye defects, rib fusion, tail defects, spina bifida, limb defects, and umbilical hernia. The data supports the conclusion that p-AP and o-AP are teratogenic in Syrian golden hamsters without compromising maternal health. As indicated in the discussion of the study,

> Maternal health was not compromised following treatment with increasing doses of p-AP, o-AP, or m-AP. Normal levels of activity and appetite were maintained by the dams. There was no evidence of maternal disease, characterized by listlessness, hair loss, diarrhea, or overt weight loss, during the course of experimentation. The teratogenicity of p-AP may be related to the formation of a reactive quinone metabolite which can readily bind macromolecules.

This study lacks replication, as there were no additional developmental toxicity studies of APAP in Syrian golden hamsters.

F. Labeling of APAP Safety During Pregnancy

As a teratologist, I am familiar with the FDA pregnancy categories that were required for prescription drugs from 1979 until 2015[397].The pregnancy categories incorporate work done in the field of teratology to identify the teratogenic potential of pharmaceuticals taken in pregnancy. Over the course of my career at medical institutions within the Texas Medical Center and at Dell Pediatric Research Institute I have been routinely consulted by clinicians about the safety of various medications in pregnancy, including the various pregnancy categories. I have conducted drug safety studies that were submitted to the FDA for pregnancy category labeling support. The pregnancy categories were used by healthcare providers to quickly assess the safety of drugs in pregnancy. There were five categories – A, B, C, D, and X – that summarized a medication's risk to the fetus as described in the table below:

[397] Pernia S, DeMaagd G. The New Pregnancy and Lactation Labeling Rule. P T. 2016 Nov;41(11):713-715. PMID: 27904304; PMCID: PMC5083079; Gruber M. F. The FDA pregnancy lactation and labeling rule – Implications for maternal immunization. Vaccine, 33 (2015), pp. 6499-6500, 10.1016/j.vaccine.2015.05.107.

A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. **OR** animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

Table 11. FDA Pregnancy Categories[398]

Rarely would a drug be assigned Category A since it is almost always unethical to perform controlled studies in pregnant women. As a result, Category B was generally presumed to be safe in pregnancy. Conversely, Category C was generally accepted as not safe in pregnancy requiring healthcare providers to consider the seriousness of the condition to be treated and the risk of not treating the condition relative to the risk to the fetus.

I reviewed the label for the prescription drug Ofirmev. In 2009, Cadence Pharmaceuticals, Inc. submitted a New Drug Application for an intravenous APAP drug, Ofirmev, prompting the FDA to evaluate APAP's teratogenic risks and designate its pregnancy category *for the first time*.[399] I reviewed the comments of the Ofirmev Maternal Health Team (MHT) and Pharmacology reviewers in connection with the consideration of the Ofirmev application and labeling. The Ofirmev MHT Review states, "Acetaminophen was approved by the FDA in 1951, prior to the 1979 regulations that established pregnancy categories, **and there are no approved acetaminophen containing products labeled with a pregnancy category based on acetaminophen content** and any acetaminophen-associated risk." (emphasis added)[400] One of the Ofirmev Pharmacology reviewers commented, "To my knowledge, a drug product label for acetaminophen as a stand alone prescription drug product has not previously been approved by the FDA."[401]

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[398] https://www.fda.gov/media/133262/download

[399] Prior to 2010, FDA approved and assigned pregnancy categories to combination APAP drugs, including Vicodin, Ultracet and Percocet. However, prior to 2010, "there [were] no approved acetaminophen-containing products labeled with a pregnancy category *based on acetaminophen content and acetaminophen-associated risk*." Ofirmev Other Review(s) at 8

[400] Ofirmev Maternal Health Team (MHT) Review at 3

[401] Ofirmev Pharmacology Review(s) at 5

The label of Ofirmev includes data from testing in mice. Briefly, the Ofirmev label documents reduced fecundity and abnormal sperm resulting from oral APAP exposure in mice at clinically relevant dosages, based on maximum human daily dosages (MHDD):

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.
This label documents "reduced number of litters per mating pair" which indicates a reduced capacity to produce offspring at a therapeutically relevant exposure (1.7X MHDD) in mice. In my opinion, a "reduced number of litters per mating pair" is consistent with a reduced capacity to produce offspring and "increased percentage of abnormal sperm" are evidence of reproductive toxicity and would not permit a pregnancy category B designation.

The Ofirmev label also documents fetotoxicity resulting from oral APAP exposure in rats at clinically relevant dosages:

> While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received **oral** acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.[402]

This label also documents "evidence of fetotoxicity" at a therapeutically relevant exposure (0.85X MHDD) in rats. Ofirmev was approved by the FDA on November 2, 2010. OTC APAP, including Tylenol, which contains the same active ingredient acetaminophen (APAP) was never shown to be safe in preclinical safety or NTP animal studies, and preclinical studies never supported pregnancy category B labeling. Pregnancy category B indicates that animal reproduction studies have not demonstrated a risk to the fetus, but there are no well-controlled studies in pregnant women. I opine that "evidence of fetotoxicity" is not the same as "animal reproduction studies have not demonstrated a risk to the fetus." The Ofirmev label states: "Pregnancy: Category C" and "Use only if clearly needed."[403]

[402] Ofirmev Label (rev. 11/2010).
[403] Ofirmev Label (rev. 11/2010).

This designation is further described on the Ofirmev label, which explains there are "no studies of intravenous acetaminophen in pregnant women" and "[a]nimal reproduction studies [had] not been conducted with IV acetaminophen".[404] In fact, the Ofirmev label's Pregnancy section only references epidemiological and preclinical studies of *orally* administered APAP. Therefore, to the extent the FDA evaluated the teratogenic risks of stand-alone, oral APAP, it determined those risks are appropriately described by pregnancy category C.

I also reviewed the label for Ultracet as well as the publicly available labeling history on the FDA's website, a combination prescription oral drug containing acetaminophen and tramadol hydrochloride.[405] Ultracet was first approved by the FDA in 2001 and was designated as pregnancy category C.[406] Ultracet is manufactured by Janssen Pharmaceutical Companies, a Johnson & Johnson company. Although, unlike Ofirmev, Ultracet is a combination drug, the Ultracet label was modified at some point between October 18, 2013 and December 16, 2016 to specifically include animal data specific to stand-alone acetaminophen.[407] An excerpt from the 2016 Ultracet Label is shown below:

> **Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately 1.3 times the maximum human daily dose (MRHD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately 1.9 times the MHDD. In mice treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproduction were seen in a continuous breeding study. A reduction in number of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.**

The 2023 Ultracet Label contains the same APAP-specific language as the 2016 version.[408] This label documents "reduction in number of litters," "retarded growth and abnormal sperm" in offspring and "reduced birth weight in the next generation." The endpoints clearly support reproductive and developmental toxicity and are consistent with "manifestations of deviant development", as defined in Wilson's Principles. In short, since 2016, a Johnson & Johnson prescription pharmaceutical drug containing APAP has contained references to animal studies showing adverse effects on the fetus at clinically relevant doses of acetaminophen and a statement that pregnant women should be advised of the potential risks to a fetus based upon this animal data.

I reviewed deposition transcripts and exhibits of JJCI witnesses. Even though the FDA replaced the traditional pregnancy categories in 2015, the deposition testimony of JCCI witnesses and JJCI's own

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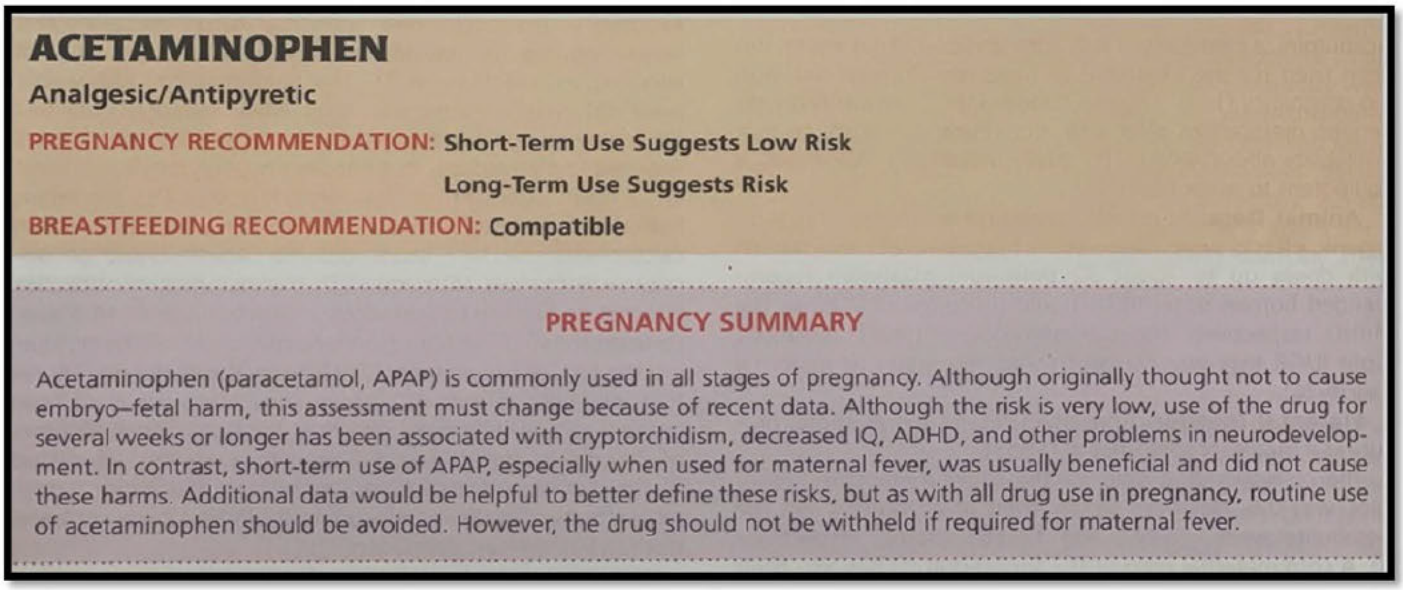
[404] *Id.* at § 8.1
[405] Ultracet Label (rev. 2/2023).
[406] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process
[407] Ultracet Label (rev. 12/2016);
[408] Ultracet Label (rev. 2/2023).

documents post-2015 reveal that the FDA pregnancy categories have retained their relevance and influence. For example, as recently as January 2023, JJCI was apparently trying to determine [redacted] FDA determined the pregnancy category for APAP.[409] The same document reveals that JJCI's internal Professional Tylenol Document represents that OTC APAP [redacted] The email exchange [redacted], even though Briggs 2022 was available at that time, which warns that APAP has been associated with fetal harm, including ADHD and other neurodevelopmental problems.[411]

I reviewed the Acetaminophen section of Briggs 2022, which states, "Acetaminophen (paracetamol, APAP) is commonly used in all stages of pregnancy. **Although originally thought not to cause embryo-fetal harm, this assessment must change because of recent data**." (emphasis added). The pertinent portions of Briggs 2022 are shown below:



ACETAMINOPHEN

Analgesic/Antipyretic

PREGNANCY RECOMMENDATION: **Short-Term Use Suggests Low Risk**
Long-Term Use Suggests Risk

BREASTFEEDING RECOMMENDATION: **Compatible**

PREGNANCY SUMMARY

Acetaminophen (paracetamol, APAP) is commonly used in all stages of pregnancy. Although originally thought not to cause embryo–fetal harm, this assessment must change because of recent data. Although the risk is very low, use of the drug for several weeks or longer has been associated with cryptorchidism, decreased IQ, ADHD, and other problems in neurodevelopment. In contrast, short-term use of APAP, especially when used for maternal fever, was usually beneficial and did not cause these harms. Additional data would be helpful to better define these risks, but as with all drug use in pregnancy, routine use of acetaminophen should be avoided. However, the drug should not be withheld if required for maternal fever.

I reviewed JJCI's Company Core Data Sheets (CCDS) for APAP. The 2013 APAP CCDS stated: [redacted] that examined the effects of prenatal exposure to APAP on neurodevelopment.[412] Candeias-Hernandez et al. published a systematic review with citation tracking that examined the history of experiments on the safety of acetaminophen.[413] The study authors showed that there were abundant studies demonstrating that, at therapeutic doses, APAP did not pose a significant risk of pediatric liver toxicity, but the authors also reported that there were no published studies demonstrating the safety of APAP during neurodevelopment.

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[409] APAP-JJCI-0001025654-25657; Exh. 27 to [redacted] Dep.
[410] Briggs, G., et al, (1990) Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk (3rd edition).
[411] Briggs, G., et al, (2022) Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk (12th edition).
[412] Exhibit 11 to Deposition of [redacted]; 2013 Company Core Data Sheet on Paracetamol at sec. 4.6.
[413] Cendejas-Hernandez et al. Paracetamol (acetaminophen) use in infants and children was never shown to be safe for neurodevelopment: a systematic review with citation tracking. Eur J Pediatr. 2022 May;181(5):1835-1857. doi: 10.1007/s00431-022-04407-w. Epub 2022 Feb 17. PMID: 35175416; PMCID: PMC9056471